

A23



(11) **EP 1 153 616 A1**

(12) **EUROPEAN PATENT APPLICATION**  
published in accordance with Art. 158(3) EPC

(43) Date of publication:  
14.11.2001 Bulletin 2001/46

(51) Int Cl.7: **A61K 47/36, A61K 47/10,**  
**A61K 47/26, A61K 9/20**

(21) Application number: **00902958.8**

(86) International application number:  
**PCT/JP00/00806**

(22) Date of filing: **14.02.2000**

(87) International publication number:  
**WO 00/47233 (17.08.2000 Gazette 2000/33)**

(84) Designated Contracting States:  
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU**  
**MC NL PT SE**  
Designated Extension States:  
**AL LT LV MK RO SI**

(72) Inventors:  

- NISHII, Hiroyuki  
Takatsuki-shi, Osaka 569-1029 (JP)
- KOBAYASHI, Hirohisa  
Ibaraki-shi, Osaka 567-0824 (JP)
- OTODA, Kazuya  
Takarazuka-shi, Hyogo 665-0877 (JP)

(30) Priority: **15.02.1999 JP 3542999**

(71) Applicant: **Sumitomo Pharmaceuticals Company,**  
**Limited**  
**Osaka-shi, Osaka 541-8510 (JP)**

(74) Representative: **Cresswell, Thomas Anthony**  
**J.A. Kemp & Co.**  
**14 South Square**  
**Gray's Inn**  
**London WC1R 5JJ (GB)**

(54) **TABLETS QUICKLY DISINTEGRATED IN THE ORAL CAVITY**

(57) There is provided a tablet preparation showing quick disintegratability in the mouth and good sensory acceptability and yet having an adequate strength to re-

sist damage in the course of distribution. Each tablet comprises a starch, a water-soluble excipient and a medicament and does not substantially contain a binder other than starch.

EP 1 153 616 A1

## Description

## TECHNICAL FIELD

- 5 [0001] This invention relates to a quick-disintegrating tablet preparation exhibiting rapid disintegratability or solubility in the mouth with little water or even without water.

## BACKGROUND ART

- 10 [0002] Heretofore known is a variety of oral dosage forms but few reflect sufficient attention to the ease of taking by the patient and there is a demand for dosage forms suited to the aged, children, and seriously ill patients who are frequently poor in compliance. For example, tablets and capsules are the dosage forms used most universally in view of the accuracy of dosage, physicochemical stability, and even the cost of manufacture but, among patients, not a few dislike those dosage forms because of their untoward mouth-feel and tendencies toward getting caught in the throat.
- 15 Powders and granules may not be completely swallowed, leaving residues in the mouth and giving a lingering unpleasant after-taste. It is acknowledged that liquid dosage forms such as syrups are suitable for both the aged and children but divided dosing from a graduated bottle is not only onerous to geriatric, pediatric, or seriously ill patients but cannot be expected to insure the accuracy of dosage. Drawbacks in terms of physicochemical stability have also been noted.
- 20 [0003] Recent years have witnessed the development of many technologies directed to the pharmaceutical dosage form which would disintegrate quickly in the mouth and have both the accuracy of dosage and physicochemical stability of tablets and capsules and the ease of ingestion of syrups in one [JP Kokai H9-309821, JP Kokai H9-309822, WO93/12769, JP Kohyo H7-501829].
- 25 [0004] However, the above-mentioned technologies are not satisfactory in assuring the stability of medicaments because comparatively large amounts of water must be used or are deficient in assuring a sufficient product strength to resist damage in the course of distribution. Furthermore, some products have difficulties in handling, while others require a complicated manufacturing process or a special production equipment. Technologies suited for more universal exploitation have been disclosed in JP Kokai H10-182436 and JP Kokai H9-71523, for instance, but there is still room for improvement in the quick disintegratability in the mouth.

## DISCLOSURE OF INVENTION

- 30 [0005] The object of this invention is to provide a tablet preparation which can be easily manufactured by means of the conventional production equipment and without requiring any extraordinary pharmaceutical expertise, insures quick disintegratability in the mouth and good sensory acceptability and yet has a suitable degree of strength to resist damage in the course of distribution.
- 35 [0006] The inventors did intensive investigations for accomplishing the above object and found that by using a starch and a water-soluble excipient in combination as the formulation additive, tablets adapted to disintegrate in the mouth within 1 minute and yet having practically useful hardness can be provided notwithstanding the common belief that such tablets can hardly be manufactured with the conventional compression machine. The finding led to the development of this invention. In particular, the effect derived from the formulation of starch in terms of disintegratability and sensory acceptability is quite pronounced as compared with the use of the conventional disintegrators such as low-substitution-degree hydroxypropylcellulose, carboxyethylcellulose calcium, croscopolvidone, etc. Indeed, this was a surprising finding which could never be anticipated from the state-of-the art information.
- 40 [0007] This invention, therefore, relates to the following tablet preparations.
- 45 [1] A tablet preparation characterized by its comprising a starch, a water-soluble excipient and a medicament and substantially not containing a binder other than starch.
- [2] The above-mentioned tablet preparation [1] wherein the starch is at least one member selected from the group consisting of corn starch, potato starch, wheat starch and rice starch.
- 50 [3] The above-mentioned tablet preparation [1] or [2] wherein the water-soluble excipient is at least one member selected from the group consisting of mannitol and lactose.
- [4] The above-mentioned tablet preparation [1]-[3] wherein the water-soluble excipient is mannitol.
- [5] The above-mentioned tablet preparation [1]-[4] wherein the total amount of starch and water-soluble excipient is not less than 50%.
- 55 [6] The above-mentioned tablet preparation [1]-[5] wherein the amount of the medicament is not more than 50%.
- [7] The above-mentioned tablet preparation [1]-[6] wherein the formulating amount of starch with respect to the total amount of starch and water-soluble excipient is not less than 5%.
- [8] The above-mentioned tablet preparation [1]-[7] wherein the formulating amount of starch with respect to the

total amount of starch and water-soluble excipient is 5-50%.

[0008] For use in this invention, the starch includes various starches which can be formulated in pharmaceutical products, such as corn starch, potato starch, wheat starch and rice starch. The water-soluble excipient is not particularly restricted but includes sugar alcohols and sugars which elicit refreshing sweetness sensations on ingestion, preferably mannitol or lactose, more preferably mannitol.

[0009] The active ingredient or medicament is not particularly restricted insofar as it is intended for oral administration but includes, to mention a few examples of medicaments to which this invention can be applied with particular advantage, antipyretic-antiinflammatory agents such as indomethacin, ibuprofen, ketoprofen, acetaminophen, aspirin, isopropylantipyrine, etc.; antihistaminics such as diphenylpyraline hydrochloride, chlorpheniramine maleate, cimetidine, isothipendyl hydrochloride, etc.; cardiovascular drugs such as phenylephrine hydrochloride, procainamide hydrochloride, quinidine sulfate, isosorbide dinitrate, etc.; antihypertensives such as amlodipine besylate, arotinolol hydrochloride, tranquilizers such as sulpiride, diazepam, valproic acid, lithium carbonate, tandospirone citrate, etc.; antibiotics such as cefalexin, ampicillin, etc.; peptides or proteins such as insulin, vasopressin, interferon, interleukin-2, urokinase, and various growth factors, e.g. human growth hormone etc.; and other drugs such as theophylline, caffeine, carbapentane citrate, phenylpropanolamine hydrochloride, etidronate disodium, cetirizine hydrochloride, droxidopa and so forth.

[0010] The tablet preparation of this invention does not contain a binder other than starch in any substantial amount, for binders other than starch detract from the effect of this invention, namely attainment of tablets which disintegrate in the mouth substantially within one minute. The binder other than starch which is substantially not contained in the preparation of this invention includes but is not limited to polyvinyl alcohol, polyvinylpyrrolidone, hydroxypropylmethylcellulose, hydroxypropylcellulose, agar and gelatin. The term 'substantially' as used herein means that the formulation of such a binder is permissible unless its content is large enough to antagonize the effect of this invention.

[0011] The pharmaceutical preparation of this invention may contain, in addition to said ingredients, various nontoxic, inert additives which are in routine use in the pharmaceutical field. As such additives, various substances which will not interfere with the effect of this invention and are generally used as pharmaceutical additives can be mentioned. For example, excipients such as xylitol, sorbitol, trehalose, glucose, sucrose, talc, kaolin, calcium hydrogenphosphate, calcium sulfate, calcium carbonate, crystalline cellulose, etc.; lubricants such as magnesium stearate, calcium stearate, sodium stearyl fumarate, light silicic anhydride, etc.; disintegrators such as carboxymethylcellulose calcium, low-substitution-degree hydroxymethylcellulose, etc.; and other formulation additives such as corrigents, antiseptics, stabilizers, antistatic agents, effervescent agents and coloring agents.

[0012] While lubricants, in particular, are used in the manufacture of tablets in accordance with this invention, magnesium stearate and sodium stearyl fumarate are advantageous.

[0013] High-sweetness artificial sweeteners such as aspartame, saccharin sodium, stevia, etc. and flavoring agents such as peppermint, spearmint, menthol, lemon, orange, grapefruit, pine, fruit, yogurt, etc. can also be incorporated, and may contribute to a more favorable sensory acceptability in some instances.

[0014] The mean particle diameter of said starch, water-soluble excipient or medicament is not particularly restricted but as far as the water-soluble excipient is concerned, the range of 10-500  $\mu\text{m}$  is preferred and that of 30-200  $\mu\text{m}$  is still more preferred. If the particle diameter is too large, compressibility will be adversely affected so that the tablet strength tends to decrease. Conversely if the particle diameter is too small, disintegrability will be seriously compromised, although improvements in compressibility will be obtained.

[0015] The total content of the starch and water-soluble excipient in the preparation is preferably not less than 50%, more preferably not less than 70%.

[0016] The formulating amount of the medicament or active ingredient depends on the kind of active ingredient but is usually not more than 50%, preferably not more than 30%, more preferably not more than 10%.

[0017] The formulating amount of starch based on the total content of starch and water-soluble excipient is not less than 5%, preferably 5-50%, more preferably 5-30%.

[0018] While the manufacturing technology for the tablet preparation of this invention is not particularly restricted, tablets may be manufactured by the following process.

[0019] Tablets can be obtained by blending the starch, water-soluble excipient and medicament and compressing the resulting composition. When the content uniformity of the medicament may hardly be assured because of the cohesive nature or large crystal sizes of the ingredients used, it is preferable to carry out a size alignment by a suitable technique such as milling before or after blending so that an adequate content uniformity may be assured. As an alternative, where necessary, the composition may be granulated in advance and compressed.

[0020] The tablet-forming technology is not particularly restricted but a compression tableting method using a rotary tablet machine, a single-punch tablet machine, or a hydraulic press can be employed. The compressive pressure to be applied is not particularly restricted insofar as sufficient strength may be imparted to the product tablet but is preferably not less than 50 kg.

# EP 1 153 616 A1

[0021] The shape of the tablet which can be provided in accordance with this invention is not particularly restricted but may be any of discoid, discoid R-edge, round bevel-edge, and various irregular shapes, and may be scored for breaking.

[0022] The following examples illustrate this invention in further detail, it being, however, to be understood that the scope of the invention is by no means defined thereby.

## Example 1

[0023]

Tandospirone citrate	5 mg
D-mannitol	103 mg
Corn starch	11 mg
Magnesium stearate	1 mg

[0024] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 7 mm in diameter and weighing 120 mg.

## Example 2

[0025]

Tandospirone citrate	5 mg
D-mannitol	90 mg
Corn starch	24 mg
Magnesium stearate	1 mg

[0026] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 7 mm in diameter and weighing 120 mg.

## Example 3

[0027]

Tandospirone citrate	10 mg
Lactose	150 mg
Wheat starch	37 mg
Sodium stearyl fumarate	3 mg

[0028] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 8 mm in diameter and weighing 200 mg.

## Example 4

[0029]

Arotinolol hydrochloride	5 mg
D-mannitol	101.9 mg
Corn starch	11 mg
Aspartame	1 mg
Flavoring agent	0.1 mg
Sodium stearyl fumarate	1 mg

[0030] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 7 mm in diameter and weighing 120 mg.

# EP 1 153 616 A1

## Example 5

[0031]

Amlodipine besylate	5 mg
D-mannitol	103 mg
Corn starch	11 mg
Magnesium stearate	1 mg

[0032] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 7 mm in diameter and weighing 120 mg.

## Example 6

[0033]

Amlodipine besylate	5 mg
D-mannitol	91 mg
Corn starch	23 mg
Magnesium stearate	1 mg

[0034] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 7 mm in diameter and weighing 120 mg.

## Example 7

[0035]

Amlodipine besylate	5 mg
D-mannitol	101.9 mg
Corn starch	11 mg
Aspartame	1 mg
Flavoring agent	0.1 mg
Sodium stearyl fumarate	1 mg

[0036] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 7 mm in diameter and weighing 120 mg.

## Example 8

[0037]

Amlodipine besylate	45 g
D-mannitol	869.4 g
Corn starch	96.3 g
Low-substitution-degree hydroxypropylcellulose	32.4 g
Aspartame	9 g
Light silicic anhydride	5.4 g
Flavoring agent	0.9 g
Sodium stearyl fumarate	21.6 g

[0038] A portion (6.3 g) of corn starch, among the above ingredients, was taken and dispersed in purified water, and the dispersion was gelatinized by warming to prepare 630 g of 1% starch size. A spray granulator (RABO-1, manufac-

# EP 1 153 616 A1

tured by Paulex) was charged with amlodipine besylate, D-mannitol, the remainder (90 g) of corn starch, low-substitution-degree hydroxypropylcellulose, aspartame and light silicic anhydride, followed by mixing, and the 1% starch size was added. The granulation was dried and transferred to a V-mixer (Model S-5, manufactured by Tsutsui Rikagaku) in which the flavoring agent and sodium stearyl fumarate were added and mixed to provide a granulation for compression tableting. This granulation was compressed with a rotary tablet machine (HT-P15A, manufactured by Hata Iron Works) at a pressure of 400 kg to provide about 9000 tablets each measuring 7 mm in diameter and weighing 120 mg.

## Comparative Example 1

[0039]

Tandospirone citrate	5 mg
D-mannitol	114 mg
Magnesium stearate	1 mg

[0040] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 7 mm in diameter and weighing 120 mg.

## Comparative Example 2

[0041]

Amlodipine besylate	5 mg
D-mannitol	114 mg
Magnesium stearate	1 mg

[0042] The above ingredients were blended and compressed with a hydraulic press (manufactured by Riken) at a pressure of 50 kgf to provide a tablet preparation measuring 7 mm in diameter and weighing 120 mg.

## Test Example 1

[0043] The tablets manufactured in Examples 1, 2, 5, 6 and 8 and Comparative Examples 1 and 2 were respectively tested for disintegration time and hardness with a mechanical disintegrability tester (Model NT-6H, Toyama Sangyo K.K.) and a mechanical tablet strength tester (TH-203CP, Toyama Sangyo K.K.).

[0044] Furthermore, these tablets were respectively administered into the oral cavity and the time to complete disintegration by saliva alone in the mouth was measured and recorded as oral disintegration time. Furthermore, the sensory acceptability was evaluated on the 3-grade scale of O: good, Δ: neither good nor bad, ×: bad.

[0045] The results are shown in Table 1. Thus, the tablets according to Example 1, 2, 5, 6 and 8 were invariably satisfactory in hardness and disintegration time and rated good in sensory acceptability. On the other hand, the tablets according to Comparative Example 1 were rather satisfactory in hardness but were remarkably retarded in disintegration and rated low in sensory acceptability.

[0046] The tablets of Comparative Example 2 were also slightly low in hardness, showed a long disintegration time, and was rated poor in sensory acceptability.

Table 1

	Example 1	Example 2	Example 5	Example 6	Example 8	Compar. Ex. 1	Compar. Ex. 2
Hardness (kg)	4	3	4	5	3	3	2
Disintegration time (sec)	19	27	15	35	30	411	80
Oral disintegration time (sec)	20	21	17	33	14	>240	100

EP 1 153 616 A1

Table 1 (continued)

	Example 1	Example 2	Example 5	Example 6	Example 8	Compar. Ex. 1	Compar. Ex. 2
Sensory acceptability	○	○	○	○	○	×	×

EFFECTS OF INVENTION

[0047] Tablets having sufficient hardness to resist damage in the course of distribution and yet disintegrating rapidly in the oral cavity can be manufactured without resort to any extraordinary pharmaceutical expertise. As a result, elderly as well as pediatric patients who are handicapped in swallowing power are now enabled to take medicines easily even without the aid of water.

Claims

1. A tablet preparation characterized by its comprising a starch, a water-soluble excipient and a medicament and substantially not containing a binder other than starch.
2. A tablet preparation as defined in Claim 1 wherein the starch is at least one member selected from the group consisting of corn starch, potato starch, wheat starch and rice starch.
3. A tablet preparation as defined in Claim 1 or 2 wherein the water-soluble excipient is at least one member selected from the group consisting of mannitol and lactose.
4. A tablet preparation as defined in any of Claims 1-3 wherein the water-soluble excipient is mannitol.
5. A tablet preparation as defined in any of Claims 1-4 wherein the total amount of starch and water-soluble excipient is not less than 50%.
6. A tablet preparation as defined in any of Claims 1-5 wherein the amount of the medicament is not more than 50%.
7. A tablet preparation as defined in any of Claims 1-6 wherein the formulating amount of starch with respect to the total amount of starch and water-soluble excipient is not less than 5%.
8. A tablet preparation as defined in any of Claims 1-7 wherein the formulating amount of starch with respect to the total amount of starch and water-soluble excipient is 5-50%.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/00806

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> Int.Cl <sup>7</sup> A61K47/36, 47/10, 47/26, 9/20		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) Int.Cl <sup>7</sup> A61K9/20-9/46, 47/06-47/42		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO, 99/18936, A (SSP CO., LTD.), 22 April, 1999 (22.04.99) & JP, 11-116464, A	1-8
X	JP, 10-298062, A (Pfizer Pharmaceuticals Inc.), 10 November, 1998 (10.11.98) (Family: none)	1,3-6 2,7,8
Y	JP, 4-91029, A (ZERIA PHARMACEUTICAL CO., LTD.), 24 March, 1992 (24.03.92) (Family: none)	1,3,6-8 2,4,5
X	EP, 553777, A (TAKEDA CHEMICAL INDUSTRIES, LTD.), 04 August, 1993 (04.08.93)	1,2,5-8 3,4
Y	& JP, 5-271054, A & US, 5501861, A	
X	JP, 9-95447, A (Takeda Chemical Industries, Ltd.), 08 April, 1997 (08.04.97) (Family: none)	1,2,5-8 3,4
Y	JP, 8-143473, A (TANABE SEIYAKU CO., LTD.), 04 June, 1996 (04.06.96) (Family: none)	1-8
Y	JP, 8-208523, A (Gunsei Kagaku Kogyo K.K.), 13 August, 1996 (13.08.96) (Family: none)	1-8
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 25 April, 2000 (25.04.00)		Date of mailing of the international search report 16 May, 2000 (16.05.00)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)